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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of

Masahiko DOHI, et al.

Group Art Unit : 1615

Serial No.: 09/125,814

Examiner : Alysia Berman

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For: POWDERY COMPOSITION FOR NASAL ADMINISTRATION

DECLARATION UNDER 37 C.F.R. 1.132

Hon. Commissioner of Patents and Trademarks.
Washington, D.C. 20231

Sir:

I, Masahiko Dohi, c/o TEIJIN LIMITED, DDS Research Laboratories, 4-3-2 Asahigaoka, Hino, Tokyo 191-8512, Japan, do hereby declare:

That I am by profession a research scientist having earned a Master's degree in pharmaceutics from Science University of Tokyo in March 1990;

That I have been employed by TEIJIN LIMITED, Tokyo, Japan, since March 1990;

That I have been engaged in research into the development of pharmaceutical products in the same company to date;

That I am a co-inventor of the invention disclosed and claimed in the above-identified U.S. application (hereinafter referred to as "present invention" for brevity) and hence I am fully familiar therewith;

That I have read and am fully familiar with U.S. Patent 4,613,500 (herein after "Suzuki") cited against claims of the above-identified U.S. application;

That I personally conducted or supervised the conduct of all of the work reported in the examples including the comparative examples in the specification of the present application, and the results obtained are as set forth therein; and

That I carried out the following experimentation to show the differences between the present invention and Suzuki, and to explain the differences between the present invention and Suzuki.

Hereinafter, the abbreviations MCC and HPC represent water-absorbing and water-insoluble base and water-absorbing and water-soluble base, respectively, in Suzuki and water-absorbing and water-insoluble base and water-absorbing and gel-forming base, respectively, in the present invention.

The difference between Suzuki and the present invention

The difference between Suzuki's product and the present invention is the amount of drug distributed to water-absorbing and water-insoluble base. The present invention has a larger amount of drug adhered to water-absorbing and water-insoluble base than Suzuki's product. Specifically, Suzuki discloses three manufacturing methods; however, the compositions manufactured according to the three methods do not have more drug adhered to the water-absorbing and water-insoluble base than on or in the water-absorbing and water-soluble base and 70% or more of the drug adhered to the base material or 60 % or more of the drug adhered to the water-absorbing and water-insoluble base material. This difference is explained in detail as follows.

Method 1 (column 6, line 39-43 of '500): *it may be admixed with polypeptide or its derivative and a water-absorbing and water-insoluble base in*

the mechanical mixing process, followed by the above-mentioned processes of compacting, etc.

In this method, the composition is manufactured by mixing polypepride or its derivative, a water-absorbing and water-insoluble base, and a water-absorbing and water-soluble base simultaneously. In the case of mixing simultaneously, the strength of mixing influences the amount of drug adhered to the water-absorbing and water-insoluble base. In order to obtain a high amount of drug adhered to the water-absorbing and water-insoluble base, strong mixing is required. However, there is no description about the strength of mixing in Suzuki, especially mixing strongly. The effect of mixing strongly is explained by using the examples in Table 16 of the present application.

Table 16
(modified)

example	mixing method	plasma conc. (ng/mL)					AUC	estimated ratio of amount of drug adhered to water-insoluble base
		15 min	30 min	45 min	60 min	90 min	(ng/ml* min)	
example 75	simultaneously, strongly	11.2	8.5	7.1	4.8	3.2	558.0	56.5
example 76	water-insoluble base and drug firstly	12.3	9.8	9.0	8.2	5.6	735.0	74.5
example 77	dispersed and evaporated water-insoluble base and drug firstly	15.7	18.3	13.2	8.6	5.7	987.0	100.0
comparative example 68	simultaneously, weakly	7.1	5.8	4.3	3.5	2.8	378.8	38.4

The above table is table 16 modified to include the mixing methods, the AUC, and the estimated ratio of amount of drug adhered to water-insoluble base. Here, the AUC, the area under the plasma concentration – time curve, was calculated from plasma concentration value and their time after dosing by using the trapezoidal method as an index showing the drug absorbability. The

estimated ratio is calculated from the AUC by following assumption. Since example 77 of the present invention is a product manufactured by dispersing drug and water-insoluble base and evaporating, most of the drug easily adhered to water-insoluble base. Hence, the ratio of the amount of drug adhered to water-insoluble base is considerable as approximately 100 %. Supposing that most of the drug absorbed is the drug adhered to water-insoluble base, each ratio of amount of drug adhered to water-insoluble base could be shown by their ratio of AUC. Then we can estimate that 56.5 % of drug adhered to water-insoluble base in Example 75 of the present invention, produced by simultaneously, strongly mixing, and 38.4 % in Comparative Example 68, produced by simultaneously, weakly mixing. (The value of 56.5 % is from 558.0, AUC of Example 75 of the present invention, divided by 987.0, AUC of Example 77 of the present invention.)

These results show that in the present invention significantly more drug is adhered to the water-absorbing and water-insoluble base material than on the water-absorbing and water-soluble base material, as compared with the results obtained from method 1 of Suzuki. Accordingly, the composition of the present invention cannot be produced by method 1 of Suzuki.

Method 2 (column 6, line 43-46 of '500): *or a water-absorbing and water-soluble base may be introduced into the process wherein polypeptide or its derivative is mixed with a water-absorbing and water-insoluble base in the presence of water.*

In this method, polypeptide drug or its derivative, a water-absorbing and water-insoluble base, and a water-absorbing and water-soluble base are mixed in the presence of water. In the case of the presence of water, the drug

is apt to adhere to the water-absorbing and water-soluble base because polypeptides drugs are hydrophilic and dissolve in water, and also the water-absorbing and water-soluble base dissolves in water. On the other hand, the water-absorbing and water-insoluble base does not dissolve in water.

Therefore, the composition manufactured by this method has a significantly lower amount of drug adhered to water-absorbing and water-insoluble base than the product produced by method 1. Accordingly, the composition produced by this method is different from the composition of the present invention. Specifically, the composition of the present invention cannot be produced by method 2 of Suzuki.

Method 3 (column 6, line 49-53 of '500): *wherein a water-absorbing and water-soluble base is added to polypeptide or its derivative in the process in which polypeptide or its derivative is to be freeze-dried, thus both components being freeze-dried simultaneously as mentioned above.*

In this method, the product is obtained by freeze-drying drug and a water-absorbing and water-soluble base, and therefore, most of drug easily adheres to the water-absorbing and water-soluble base, as shown in the Declaration under 37 C.F.R. § 1.132 submitted on March 14, 2001. Therefore, the ratio of the amount of drug adhered to the water-absorbing and water-insoluble base can be estimated as approximately 0 %. As a result, this composition has a significantly lower amount of drug adhered to the water-absorbing and water-insoluble base than the present invention. This is explained by using the examples in the present application, as with method 1 above.

Table 14
(modified)

example	mixing method	plasma conc (pg/mL)							AUC	estimated ratio of amount of drug adhered to water-insoluble base
		15 min	30 min	45 min	60 min	90 min	120 min	180 min	(pg/ml* min)	
example 69	water-insoluble base and drug firstly	30	70	75	65	55	35	20	7912.5	77.9
example 70	water-insoluble base and drug are freeze-dried firstly	30	75	85.0	75	65	55	40	10162.5	100.0
example 71	simultaneously, strongly	25	55	60	45	35	25	15	5737.5	56.5
comparative example 65	water-soluble base and drug are freeze-dried firstly	5	15	20	10	5	0	0	975.0	9.6

The above table is table 14 modified to include the mixing methods, the AUC, and the estimated ratio of amount of drug adhered to water-insoluble base. Here, the AUC, the area under the plasma concentration – time curve, was calculated from plasma concentration value and their time after dosing by using the trapezoidal method as an index showing the drug absorbability. The estimated ratio is calculated from the AUC by following assumption.

Since example 70 of the present invention is manufactured by freeze-drying drug and water-insoluble base, most of the drug easily adhered to water-insoluble base. Hence, the ratio of the amount of drug adhered to water-insoluble base is considered to be 100 %. Supposing that most of the drug absorbed is the drug adhered to water-insoluble base, each ratio of amount drug adhered to water-insoluble could be shown by their ratio of AUC. Then, it can be estimated that 9.6 % of the drug adhered to water-insoluble

base in Comparative Example 65 of the present invention, produced by freeze-drying drug and water-absorbing and water-soluble base. This supports the above discussion that the ratio of the amount of drug adhered to water-insoluble base can be estimated as approximately 0 %. Thus, the product obtained by method 3 has a significantly lower amount of drug adhered to water-absorbing and water-insoluble base than that of the present invention.

Therefore, the composition of the present invention cannot be produced by method 3 of Suzuki.

Lastly, the order of the method to obtain a large amount of drug adhered to a water-absorbing and water-insoluble base and the estimated ratio of drug adhered to the water-insoluble base are shown on the basis of our examples as follows:

Freeze-drying the drug and the water-insoluble base, and dissolving and evaporating drug and the water-insoluble base (100%); mixing the drug and the water-insoluble base first (80%), mixing the drug, the water-insoluble base and the water-soluble base simultaneously and strongly (60%); mixing the drug, the water-insoluble base and the water-soluble base simultaneously and weakly (40%); mixing drug, the water-insoluble base and the water-soluble base in the presence of water (less than 40%); freeze-drying drug and the water-soluble base (less than 10%). Therefore, I conclude that the present invention has significantly more drug adhered to the water-insoluble base than does Suzuki, which has less than 40%.

Accordingly, Suzuki does not teach or suggest the composition of the present invention. In addition, Suzuki does not teach or suggest a process of

making the composition of the present invention. Moreover, based on the above evidence together with the evidence of record, I conclude that the present invention provides unexpectedly superior results.

I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Signed this 19 day of October, 2001

Masahiko Dohi

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Signed this 19 day of October, 2001

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